REMARKS

The Office Action

Claims 30, 31, 33, 34, 36, 37, 43, 44, 46, 47, 50, 53-62, and 64-72 are pending in this application. Claim 31 is objected to under 37 C.F.R. § 1.75, claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-62, and 64-72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, and claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-55, 57, 59, 61, and 72 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. By this reply, Applicants amend claims 30, 33, 51, and 54, cancel claims 31, 37, and 46, and address each of the Examiner's rejections.

Support for the Amendment

Support for the amendment to claims 30, 33, 51, and 54 is found in the specification at, e.g., page 9, lines 2-4; page 9 line 18, through page 10, lines 3; page 20, lines 5-8; and page 39, lines 2-8. No new matter is added by the amendment.

Objection under 37 C.F.R. § 1.75

Claim 31 is objected to under 37 C.F.R. § 1.75 as being "a substantial duplicate of claim 30" (Office Action, p. 2). Although Applicants do not concede that claims 30 and 31 are substantial duplicates, in an effort to expedite prosecution of the pending claims, Applicants have canceled claim 31. Accordingly, this objection can now be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-55, 57, 59, 61, and 72 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that "it is unclear what is encompassed by the phrase 'a region of at least 150 amino acids having at least 90% sequence identity to the corresponding of amino acid residues 1-185 of SEQ ID NO:2', and therefore it renders the claims indefinite" (Office Action, pp. 19-20; emphasis in original). This issue has been addressed by the present amendment to claim 30. Therefore, this rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-62, and 64-72 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the specification is only enabling for:

> a method of lowering cholesterol in a mammal that lacks an endogenous normally functioning apoE gene, said method comprises intravascularly administering to said mammal a recombinant replication defective adenovirus comprising a nucleic acid sequence encoding a secreted polypeptide comprising amino acid residues 1-185 of SEQ ID NO:2, wherein said nucleic acid sequence does not encode amino acids 260-299 of SEQ ID NO: 2 and said polypeptide, when expressed and secreted in said mammal, lowers the total serum cholesterol without inducing hypertriglyceridemia. (Office Action, p. 3).

Applicants respectfully disagree with the Examiner's conclusion as to the scope of enablement supported by the present specification. Yet, in an effort to expedite prosecution of the present application, Applicants have amended independent claim 30 to recite that the mammal

"expresses a functional low density lipoprotein (LDL) receptor," that the vector is "a *replication-defective adenoviral* vector," that the polypeptide is "*secreted*," and that the polypeptide has "at least 90% sequence identity to SEQ ID NO:2." Applicants believe that the scope of independent claim 30, as presently amended, and claims dependent therefrom, is fully enabled by the specification. Furthermore, Applicants note that the scope of present claim 30, and claims dependent therefrom, corresponds exactly to the scope deemed enabled by the Examiner, with the exception that the treated mammal is one that lacks an endogenous normally functioning apoE gene (Office Action, p. 3). As is discussed below, Applicants believe that present claims 30, 33, 34, 36, 43, 44, 47, 50, 53-62, and 64-72 are fully enabled without this limitation, and respectfully request that the Examiner reconsider his position with respect to the enablement of the present claims.

As is discussed above, Applicants have amended independent claim 30 so that it now corresponds to the scope deemed enabled by the Examiner, excepting only the limitation that the treated mammal is one that lacks an endogenous normally functioning apoE gene (Office Action, p. 3). As evidence that the method of present claim 30, and claims dependent therefrom, is enabled for use in a mammal that expresses an endogenous normally functioning apoE gene, Applicants provide the attached Declaration of Dr. Vassilis Zannis, which states that the methods of the invention have been used successfully and predictably in animals that possess an endogenous, normally functioning apoE, e.g., wild-type mice (see ¶ 4 of the Declaration). Furthermore, Dr. Zannis states that, in every instance tested, expression of a secreted apoE polypeptide lacking amino acids 260-299 in animals that express a functional low density lipoprotein (LDL) receptor produced a therapeutic effect, regardless of the presence or absence of a normally functioning apoE polypeptide (see ¶ 5 of the Declaration). Thus, the specification

fully enables a method of lowering cholesterol in a mammal that possesses a normally functioning apoE polypeptide, as long as the mammal expresses a functional LDL receptor, a limitation that is recited in present claim 30, and claims dependent therefrom.

Evidence of the therapeutic effect that results upon expression of a truncated apoE polypeptide is provided in ¶ 6 of the Declaration. Section (a) of ¶ 6 states that expression of apoE2-202 (corresponding to amino acids 1-202 of apoE2) in knock-in mice where the endogenous mouse apoE has been replaced by the corresponding human apoE2 (i.e., a mouse expressing a normally functioning human apoE polypeptide) resulted in a reduction in high cholesterol levels and high triglyceride levels (see Fig. 1 accompanying the Declaration). Truncated apoE polypeptides have also been shown to reduce cholesterol levels without inducing hypertriglyceridemia when expressed in normal wild-type mice. Section (b) of ¶ 6 states that injection of full-length apoE in C57BL/6 mice that express an endogenous, normally functioning apoE induces high cholesterol and high triglyceride levels, while co-injection of the mice with a mixture containing a similar dose of a full-length apoE (apoE2 or apoE4) along with truncated apoE (apoE2-202 or apoE4-202) prevents the induction of dyslipidemia (see Fig. 2 of the accompanying Declaration). Dr. Zannis attests that this result occurs because the truncated apoE has a dominant effect over the full-length apoE, and thus, clears the lipoprotein remnants that would otherwise have accumulated due to the presence of full-length apoE alone (see ¶ 6 (b) of the Declaration). Furthermore, the Declaration provides data showing that several different truncated apoE polypeptides promoted a reduction in cholesterol levels without inducing hypertriglyceridemia, and that the effect of each lasted for several days following infection of apoE-deficient mice using a recombinant adenovirus encoding the truncated apoE polypeptide (see ¶ 6 (c) and Fig. 3 of the accompanying Declaration). Lastly, the Declaration provides data

demonstrating the ability of truncated apoE polypeptides to clear cholesterol without inducing hypertriglyceridemia using a second atherogenic animal model, the apoA-I mutant animal model. Section (d) of ¶ 6 states that expression of a mutant human apoA-I, designated apoA-I[E110A/E111A], caused hypertriglyceridemia and moderated hypercholesterolemia in apoA-I-deficient mice, but that simultaneous expression of the mutant apoA-I [E110A/E111A] and a truncated apoE4-202 corrected the dyslipidemia (see Fig. 4 of the accompanying Declaration). These results clearly confirm that adenovirus-mediated administration of a truncated apoE polypeptide lacking amino acids 260-299 to a mammal that possesses a functional LDL receptor successfully reduces the mammal's cholesterol levels without inducing hypertriglyceridemia. Accordingly, Applicants respectfully submit that claims 30, 33, 34, 36, 43, 44, 47, 50, 53-62, and 64-72, as presently amended, are enabled to their full breadth.

Applicants also wish to address the Examiner's statement that "Applicants' argument [for enablement of the pending claims] may be valid for *in vitro* or cell culture expression systems, but not *in vivo*, particularly in a subject in which therapeutic effects are desired. It is still unpredictable in obtaining effective *in vivo* transgene expression levels that yield desired therapeutic effects" (Office Action, p. 15; emphasis in original). Applicants note that all of the data presented in the Declaration of Dr. Zannis was obtained from *in vivo* studies, each of which show a clear and established cholesterol-lowering therapeutic effect (in the absence of induced hypertriglyceridemia). Thus, the data presented in the Declaration provide compelling evidence in support of Applicants' position that independent claim 30, and claims dependent therefrom, are enabled to their full breadth, especially as to *in vivo* therapy. Furthermore, as is attested to in the Declaration of Dr. Zannis, expression of the truncated apoE in animals expressing a functional LDL receptor produced a therapeutic result *in every instance tested* (see ¶ of the

Declaration). Thus, Applicants submit that the *in vivo* applications of the method of present claim 30, and claims dependent therefrom, are also fully enabled.

In view of the foregoing, Applicants respectfully submit that the full breadth of present claims 30, 33-34, 36, 43-44, 47, 51, 53-62, and 64-72 is enabled by the specification, such that one skilled in the art can successfully and predictably practice the claimed invention using no more than routine experimentation. Thus, Applicants respectfully request that the rejection of claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-62, and 64-72 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for two months, to and including February 21, 2006, as February 19, 2006, falls on a Sunday and February 20, 2006, is a holiday. Applicants also enclose a check for the fee required under 37 C.F.R. § 1.17(a). If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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